Claims 1, 2, 11, and 12 were rejected under 35 U.S.C. §112, second paragraph. Claims 1 and 8-12 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Kuberasampath et al (US Patent No. 5,674,844) further in view of Ting et al (The Journal of Bone and Mineral Research, 1999, 14:80). Claim 2 was rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Kuberasampath et al further in view of Ting et al as applied to claims 1 and 8-12 and further in view of Siris et al (Osteoporis Int., 1998). Applicant respectfully traverses by amendment and argument.

**COMPLIANCE WITH THE SEQUENCE LISTING RULES.**

The Examiner indicated that the application is not in compliance with sequence rules, 37 C.F.R. §§ 1.821-1.825. A disk containing the referenced sequences in computer readable form (CRF), and a paper copy of the sequence information that has been printed from the floppy disk are provided herewith. The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

**ELECTION/RESTRICTION REQUIREMENT.**

Applicant acknowledges the Examiner's withdrawal of Groups II-XI from further consideration, pursuant to Applicant's election with traverse of Group I. Pursuant to the restriction requirement made final, Applicant cancels claims 3-7 and 13-49 with entry of this amendment. Please note, however, that Applicant reserves the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

**OBJECTION TO THE SPECIFICATION**

The Examiner objected to the specification because of an informality and suggested that at page 11, line 20, the second occurrence of "in by changes" should be deleted. Applicant thanks the Examiner for a thorough reading of the specification, and has amended the specification accordingly, thereby obviating the objection. Applicant requests withdrawal of this objection.

**OBJECTON TO THE DRAWINGS.**

The drawings were objected to by the Draftsman under 37 CFR 1.84 or 1.152. The drawings have been corrected and new drawings are submitted with this response.

**35 U.S.C. §112, SECOND PARAGRAPH REJECTIONS.**

Claims 1-2 and 11-12 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the following reasons:

1) The use of the term "change" in claim 1 was allegedly indefinite.

2) The use of the term "test agent" in claims 1-2 and 11-12 was allegedly indefinite.

3) The use of the terms "alter or alters" in claims 1-2 was allegedly indefinite.

4) The use of the language "recording test agents that alter the expression of the Nell-1 nucleic acid or the Nell-1 protein" in claim 2 was allegedly vague and confusing.

Applicant respectfully traverses these rejections by argument and amendment.

**The term "change."**

Claim 1 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because claim 1 recited "change" which the Examiner stated "is unclear as to what the applicant is referring."

Applicant has amended claim 1 to recite "detecting an expression level of said NELL-1 gene in the contacted cell where a difference in the expression level of NELL-1 in the contacted cell is compared to an expression level of NELL-1 in a cell that is not contacted indicates that said test agent is an agent that modulates bone mineralization." At page 3, lines 6-23, the specification states that the term "change" refers to a difference in expression of the NELL-1 gene between a cell that has been contacted by a test agent and a cell that has not been contacted by a test agent. Therefore, this amendment is supported in the specification and adds no new matter. The amendment obviates the rejection and Applicant requests withdrawal of this rejection.

**The term "test agent."**

Claims 1-2 and 11-12 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the four claims recited the term "test agent," which the Examiner stated "is unclear as to what the applicant is referring."

Applicant has amended claim 1 to more clearly differentiate between "test agent" and "agent that modulates bone mineralization." Dependent claims 2, 11, and 12 are consequently clarified. At page 9, lines 1-5, the specification states that term test agent is defined as an agent that is to be screened in one or more of the assays described in the application in order to identify an agent that modulates bone mineralization. Therefore, this amendment is supported in the specification and adds no new matter. The amendment obviates the rejection and Applicant respectfully requests withdrawal.

**The terms "alter or alters"**

Claims 1 and 2 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the two claims recited the term "alter or alters" which the Examiner stated "is unclear as to what the applicant is referring."

Applicant has amended claim 1 by changing "alters" to "modulates." Applicant has amended claim 2 by changing "alter" to "modulate." Support for these amendments is found in the specification at page 3, lines 6-23 where the specification states that the term alters is interchangeable with modulates. These amendments therefore add no new matter. These amendments obviate the rejection, and Applicant respectfully requests withdrawal.

**The language "recording test agents that alter the expression of the Nell-1 nucleic acid or the Nell-1 protein."**

Claim 2 was rejected under 35 U.S.C. §112, second paragraph, as allegedly vague and confusing. The Examiner stated that:

> Claim 2 is vague and confusing because it recites both "recording test agents that alter the expression of the Nell-1 nucleic acid or the Nell-1 protein;" however these appear to be the same thing. Altering the expression of the gene would inherently alter the expression of the protein. Accordingly, this language appears to be redundant. For purposes of this Office Action, the claim language has been interpreted as altering the expression of gene. If this assumption is correct, the phrase "or the Nell-1 proteins" should be deleted from the claim.

Office Action dated September 24, 2001 at page 5.

The Examiner appears to be confusing the language "expression of the NELL-1 **gene**" with "expression of the NELL-1 **nucleic acid**." As stated in the specification at page 3, lines 10-12, expression of the Nell-1 **gene** encompasses expression of the **nucleic acid** (e.g.,

mRNA) and/or expression of the **protein**. Therefore, it is not vague and confusing for claim 2 to refer to test agents that modulate expression of the Nell-1 **nucleic acid** or the Nell-1 **protein** when referring to test agents that modulate expression of the Nell-1 **gene**.

In addition, while it is true that an agent that alters expression of the mRNA **could** alter expression of the protein, one of skill in the art can envision other scenarios. One could alter the expression of protein without altering the expression of nucleic acid, e.g., with an agent that increases stability of the protein without affecting transcription. Conversely, one could alter expression of the mRNA without altering expression of the protein, e.g., with an agent that both decreases transcription and increases translation, thereby decreasing mRNA levels but not protein levels. The invention is intended to include methods for identifying at least all of these kinds of agents, and is not meant to be limited to only those agents that affect nucleic acid expression levels. In view of the above arguments, Applicant respectfully requests withdrawal of this rejection.

The foregoing amendments address issues of clarity and anteceedent basis. The amendments do not narrow the scope of the claimed invention

**35 U.S.C. §103(A) REJECTIONS.**

Claims 1 and 8-12 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Kuberasampath et al (US Patent No. 5,674,844) further in view of Ting et al (The Journal of Bone and Mineral Research, 1999, 14:80.) Claim 2 was rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Kuberasampath et al further in view of Ting et al as applied to claims 1 and 8-12 and further in view of Siris et al (Osteoporis Int., 1998).

Applicant respectfully traverses. First, because the claimed invention was invented in the U.S. prior to the publication date of Ting et al (see accompanying Declaration under 37 CFR §1.131), this reference is not available as prior art under 35 U.S.C. §102(a). Second, even if Ting et was available as prior art under 35 U.S.C. §102(a), a *prima facie* case of obviousness is clearly not met by combining Kuberasampath et al with Ting et al.

**Ting et al is not available as prior art**

The Ting et al reference was published in January of 1999. As stated by the Applicant in the accompanying Declaration of Kang Ting under 37 CFR §1.131, Applicant completed his invention in the United States by a date that is before the publication date of Ting

et al. The Ting et al reference is therefore not prior art to the instant application under 35 USC § 102(a)/103(a).

**Kuberasampath et al alone does not render obvious the inventions of claims 1 and 8-12.**

Because Ting et al is unavailable as prior art under 35 USC §102(a)/103(a), only Kuberasampath et al remains to support the Examiner's rejection of claims 1 and 8-12. This reference does not render the claimed invention obvious.

Claims 1 and 8-12 are drawn to a method of screening for an agent that modulates bone mineralization, said method comprising contacting a cell containing a NELL-1 gene with a test agent, and detecting an expression level of said NELL-1 gene in the contacted cell, where a difference in the expression level of NELL-1 in the contacted cell compared to an expression level of NELL-1 in a cell that is not contacted indicates that said test agent is an agent that modulates bone mineralization. Kuberasampath et al teaches a method of screening for candidate compounds which alter bone mass by incubating a cell in culture with a compound to assess the effects of the compound on the cell. As stated by the Examiner, **"Kuberasampath et al do not specifically teach assay methods for testing compounds which effect expression of the Nell-1 gene."** Absent any teaching of NELL-1, Kuberasampath et al alone fails to teach all of the elements of claims 1 and 8-12. Therefore, Kuberasampath et al does not render obvious the inventions of claims 1 and 8-12 and cannot be used as the basis for a rejection under 35 USC § 103(a). Applicant requests withdrawal of this rejection.

**The combination of Kuberasampath et al and Siris et al does not render claim 2 obvious.**

Claim 2 is drawn to the method of claim 1, further comprising recording agents that modulate expression of the NELL-1 nucleic acid or the NELL-1 protein in a database of modulators of NELL-1 activity or in a database of modulators of bone mineralization. As discussed in the preceding paragraph, Kuberasampath et al teaches a method of screening for candidate compounds which alter bone mass by incubating a cell in culture with a compound to assess the effects of the compound on the cell. As stated by the Examiner, **"Kuberasampath et al do not specifically teach assay methods for testing compounds which effect expression of the Nell-1 gene."**

Siris et al teaches a database that contains peripheral and central measurements of bone density, and teach relating these factors to treatment patterns and the natural history of osteoporosis. Siris et al offers no teaching or suggestion of NELL-1.

Absent any teaching or suggestion of NELL-1, the combination of Kuberasampath et al and Siris et al fails to provide all of the elements of claim 2. Therefore, the combination of Kuberasampath et al and Siris et al fails to support a *prima facie* case of obviousness. Accordingly, the rejection of claim 2 under 35 USC §103(a) should be withdrawn.

**Kuberasampath et al with Ting et al. fail to provide a motivation to combine or a reasonable expectation of success.**

Furthermore, even if Ting et al was available as prior art, the combination of Kuberasampath et al with Ting et al would not support a *prima facie* case of obviousness.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02.

The combination of Kuberasampath et al with Ting et al fails to provide a motivation to combine or a reasonable expectation of success. Kuberasampath et al teaches methods for identifying agents that affect the level of morphogens that in turn prevent bone loss and/or increase bone formation. See Kuberasampath et al, cols 36-38. Morphogens are defined at col. 16, line 30-37 as proteins that are "capable of inducing the developmental cascade of cellular and molecular events that culminate in the formation of new, organ specific tissue and comprises at least the conserved C-terminal six cysteine skeleton or its functional equivalent."

Ting et al teaches that human NELL-1 is preferentially expressed in cranial intramembranous bone and neural tissue and is up-regulated during unilateral premature closure of the coronal suture. See Ting et al, Abstract. **Nowhere does Ting et al teach that NELL-1 is a morphogen or has properties of morphogens as described by Kuberasampath et al.**

For example, Ting et al does not describe NELL-1 as capable of inducing the developmental cascade of cellular and molecular events that culminate in the formation of new, organ specific tissue. Instead, Ting et al states that **"The precise role of this gene is unknown."** See Ting et al, Abstract.

In addition, Ting et al does not teach that NELL-1 comprises the conserved C-terminal six cysteine skeleton or its functional equivalent as described by Kuberasampath et al. Instead, Ting et al teaches that NELL-1 contains six epidermal growth factor (EGF)-like repeats. See Ting et al, page 81, first column, last paragraph.

Given the teaching of Ting et al regarding NELL-1, one of skill in the art would not recognize NELL-1 to be a morphogen as described by Kuberasampath et al. In view of this, one of skill in the art would not be motivated to combine NELL-1 as taught by Ting et al with the screening method taught by Kuberasampath et al.

Further, failing any teaching or suggestion that NELL-1 is a morphogen as described by Kuberasampath et al, one of skill in the art would have no expectation of success in screening for agents that alter bone mass (e.g., bone mineralization) if one of skill were to combine NELL-1 as taught by Ting et al with the screening method taught by Kuberasampath et al. Therefore, a *prima facie* case of obviousness is clearly not met by combining Kuberasampath et al with Ting et al and Applicant requests withdrawal of the 35 USC §103(a) rejection of claims 1, 2, and 8-12.

**A rejection based on an hindsight reconstruction is improper.**

Applicant respectfully points out that it is the instant patent application that teaches that NELL-1 plays a role in bone formation, e.g., bone mineralization. The Examiner is mistaken when she states that "the Nell-1 gene, as taught by Ting et al, is also known to produce a protein that enhances bone mineralization..." See 9/24/01 Office Action, page 7, last three lines. Nowhere does Ting et al teach that NELL-1 plays a role in bone formation. Instead, Ting et al teach that NELL-1 is preferentially expressed in cranial intamembranous bone and neural tissue and is up-regulated during unilateral premature closure of the coronal suture.

Applicants respectfully submit that the Examiner's 103(a) rejection constitutes improper hindsight reconstruction. As recently stated by the Court of Appeals for the Federal Circuit:

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. *See Dembiczak* , 175 F.3d at 999, 50 USPQ2d at 1617 . **Close adherence to this methodology is especially important in cases where the very ease with which the invention can be**

> **understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher."** Id. *(quoting W.L. Gore & Assocs., Inc. v. Garlock, Inc.* 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983)). [emphasis added] (*In Re Werner Kotzab,* 217 F.3d 1365, 55 USPQ2d 1313, ____ (Fed. Cir. 2000)

In the instant case, "casting the mind back to the time of invention" we find that Kuberasampath et al teaches screening methods for identifying agents that affect the level of morphogens; morphogens are defined as proteins that are "capable of inducing the developmental cascade of cellular and molecular events that culminate in the formation of new, organ specific tissue and comprises at least the conserved C-terminal six cysteine skeleton or its functional." As the Examiner concedes in the instant Office Action, Kuberasampath et al fail to teach using the screening methods with NELL-1. This failure is not remedied by Ting et al. Ting et al does not teach that NELL-1 is a morphogen or has properties of morphogens as described by Kuberasampath et al. Rather, Ting et teaches that, e.g., the function of the NELL-1 gene is unknown.

The only teaching that NELL-1 plays a role in bone formation, e.g., bone mineralization, is found in the present application. As indicated above, using the Applicant's own teaching comprises improper hindsight reconstruction. This cannot support a *prima facie* case of obviousness. As in *Kotzab*, the Examiner in the present case has failed to identify motivation, suggestion or teaching of the desirability of making the specific combination that was made by the Applicants and claimed herein. Accordingly, the Examiner has failed to make a *prima facie* case of obviousness and the rejection under 35 U.S.C. §103(a) should be withdrawn.

## CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3505, direct.

Respectfully submitted,

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## APPENDIX A

## VERSION WITH MARKINGS TO SHOW CHANGES MADE TO THE SPECIFICATION AND CLAIMS OF 09/412,297 WITH ENTRY OF THIS AMENDMENT

### IN THE SPECIFICATION

**At the fourth full paragraph found at page 5, line 27-29:**

The terms "NELL-1 cDNA" and "NELL-1" genomic DNA refer to the cDNA and genomic DNA as disclosed by Watanabe et al. (1996) Genomics 38 (3): 273-276; Ting et al. (1999) J Bone Mineral Res, 14: 80-89; and GenBank Accession Number U57523 (SEQ ID NO: 2).

**At the third full paragraph found at page 11, lines 20-26:**

Expression levels of a gene can be altered by changes in ~~by changes in~~ the transcription of the gene product (i.e. transcription of mRNA), and/or by changes in translation of the gene product (i.e. translation of the protein), and/or by post-translational modification(s) (e.g. protein folding, glycosylation, etc.). Thus preferred assays of this invention include assaying for level of transcribed mRNA (or other nucleic acids derived from the NELL-1 gene), level of translated protein, activity of translated protein, etc. Examples of such approaches are described below.

### IN THE CLAIMS

1. (Amended) A method of screening for an agent that ~~alters~~ modulates bone mineralization, said method comprising:

contacting a cell containing a NELL-1 gene with a test agent; and

detecting ~~a change in the~~ an expression level of said NELL-1 gene in the contacted cell ~~as compared to the expression of the NELL-1 gene in a cell that is not contacted with said test agent,~~ where a difference in the expression level of NELL-1 in the contacted cell ~~and~~ compared to an expression level of NELL-1 in ~~the~~ a cell that is not contacted indicates that said test agent is an agent that modulates bone mineralization.

2. (Amended) The method of claim 1, further comprising recording ~~test~~ agents that ~~alter~~ modulate expression of the NELL-1 nucleic acid or NELL-1 protein in a

database of modulators of NELL-1 activity or in a database of modulators of bone mineralization.

## APPENDIX B

**CLAIMS PENDING IN USSN 09/412,297 WITH ENTRY OF THIS AMENDMENT**

1. (Amended) A method of screening for an agent that modulates bone mineralization, said method comprising:

contacting a cell containing a NELL-1 gene with a test agent; and

detecting an expression level of said NELL-1 gene in the contacted cell, where a difference in the expression level of NELL-1 in the contacted cell compared to an expression level of NELL-1 in a cell that is not contacted indicates that said test agent is an agent that modulates bone mineralization.

2. (Amended) The method of claim 1, further comprising recording agents that modulate expression of the NELL-1 nucleic acid or NELL-1 protein in a database of modulators of NELL-1 activity or in a database of modulators of bone mineralization.

8. The method of claim 1, wherein said level of NELL-1 is detected by determining the expression level of a NELL-1 protein in said biological sample.

9. The method of claim 8, wherein said detecting is via a method selected from the group consisting of capillary electrophoresis, a Western blot, mass spectroscopy, ELISA, immunochromatography, and immunohistochemistry.

10. The method of claim 1, wherein said cell is cultured ex vivo.

11. The method of claim 1, wherein said test agent is not an antibody.

12. The method of claim 1, wherein said test agent is not a protein.